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INCIDENCE OF CNS OXYGEN TOXICITY WITH MILD HYPEROXIA: A LITERATURE AND DATA REVIEW

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14. ABSTRACT

Central nervous system (CNS) oxygen toxicity manifests in a number of ways, from mild symptoms to loss of consciousness and seizure. The available data were reviewed in 1986 and predictive models were proposed. However, the outcomes of many mildly hyperoxic dives ($1.0<PO_2<1.7$ atm) conducted since 1986 may be poorly predicted by the models. This report examines the correspondence of five published models to all available data, those with which the models were developed and those from more recent experiments. Differences within the data sets for mild hyperoxia are examined, and empirical probabilities of CNS oxygen toxicity are suggested. The published models overestimate experimental incidence of CNS oxygen toxicity at low PO_2 where CNS oxygen toxicity is extremely rare. For training dives, adverse events are more common, probably as a result of CO_2 retention by trainee divers, and data from experimental and training dives cannot be combined. During a MK 16 dive within the decompression tables, probability $p\leq 1.5\%$ (95% confidence interval) of any symptom of CNS oxygen toxicity with N_2O_2, and $p\leq 0.4\%$ with HeO_2. For a 240-minute dive with $PO_2 = 1.4$ atm, $p\leq 1.7\%$ for a definite CNS oxygen toxicity event. However, if CO_2 is poorly controlled, $p\leq 10\%$.

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INTRODUCTION

Central nervous system (CNS) oxygen toxicity manifests in a number of ways, from mild symptoms to loss of consciousness and seizure. Because loss of consciousness underwater is easily fatal and sometimes occurs without prior symptoms, divers must take precautions to avoid oxygen exposures that might provoke it. However, diving with oxygen partial pressure (PO_2) greater than one atmosphere can be safe and is highly advantageous under many circumstances. Conventional wisdom has held that a safe oxygen partial pressure threshold lies somewhere between 1.3 and 1.6 atm and that risk is a function of time at higher oxygen partial pressures, but conventional wisdom needs empirical back-up. With increased diving of rebreather UBAs that control PO_2 independent of depth but that are not immune from transient periods at higher PO_2 than their targets has come increasing concern about risks of those overshoots.

Systematic investigation of CNS oxygen toxicity during hyperbaric exposures with 100% oxygen has been conducted under both dry and immersed conditions. In 1993, Harabin[1] tabulated data from the 14 known studies published between 1945 and 1986. Six papers presented data from exposures in dry hyperbaric chambers,[2–7] where CNS oxygen toxicity risk is lower than that in the water,[8, 9] and ten reported on studies done in immersed subjects.[4,6,10–17] Some of those studies had been designed to determine acceptably safe time limits for single depth exposure[15] or exposures with deeper excursions, [16, 17] limits which appear in the U.S. Navy Dive Manual.[18]

No dive series since 1993 have been conducted specifically to study CNS oxygen toxicity. However, mildly hyperoxic dives have been directed at pulmonary oxygen toxicity[19–29] and at development of decompression tables for underwater breathing apparatus (UBA) with controlled PO_2.[30–36] Additionally, safety information from training dives with oxygen rebreather UBAs has been published.[37]

Models permit interpolation between, and occasionally extrapolation beyond, measured conditions. Harabin proposed three risk model formats, two exponential[9, 38, 39] and one autocatalytic.[39] More recently, Arieli et al. proposed a different exponential model.[40] Harbin fitted her models variously to all single-depth exposures conducted between 1970 and 1986,[38] to groupings of single- and multiple-depth exposures for different conditions (rest wet or dry, wet rest or exercise, pre-1970 or newer studies,[9] and to all post-1970 immersed single- or multiple-depth exercise data.)[39] Arieli[40] fitted to post-1970, single-depth exposure data, with or without additional data obtained from open-water training dives.[37]

This report first compares model predictions with available data, including those collected since 1995. Although CNS oxygen toxicity is not unknown when PO_2 is less than 1.7 atm,[16, 17, 37] experience suggests that the models overestimate the risk in this range.[30, 31] Second, then, this report provides summary statistics for CNS events during mildly hyperoxic dives. The goal is to provide model-independent, data-driven estimates of CNS oxygen toxicity risk under mild hyperoxia.

METHODS

MODEL COMPARISON

Harabin's 1993 data tabulation[1] in electronic format was split into its separate studies, and, for some data, compared to the original publications.[12,15–17] Studies conducted before 1970 were treated separately from those done later because the outcomes have been shown to be very different.[9] Cold water dive records were added from some publications.[13, 16] Dives conducted to assess pulmonary oxygen toxicity were also added,[19–29] as were the published data from training dives.[37] Dives conducted to assess decompression tables[30–36] were entered only in aggregate based on published summaries.[31]

When dive series included repeated dives, the two dives were considered to be a single dive if the surface interval was less than 4 hours.

Predicted probabilities of CNS events from all available data were calculated using the five models listed below ("Model descriptions"): Harabin's 1995 autocatalytic model,[39] Harabin's two exponential model formulations, [9, 38, 39] and Arieli's exponential model with both published parameter sets.[40] Model predictions were compared to experimental results for the calibration data set and for all available data divided by dive profile. When an experimental dive was interrupted by CNS oxygen toxicity, the planned duration, not the actual one, was used in calculating the modeled probability of an event. For example, if a 360-minute dive was interrupted by a CNS hit at 250 minutes, say, the risk was calculated for a 360-minute dive.

Model descriptions

For failure rate (instantaneous risk) models, the probability that an undesirable event will occur by time t is given as

$$P(t) = 1 - e^{-R(t)},$$

$$\text{where } R(t) = \int r(t)\, dt, \text{ the integral of instantaneous risk } r(t).$$

The expressions for instantaneous risk are given below for the three failure-rate models applied.

Note that normobaric exposure to 100% oxygen give a PO_2 of 1 atm. In other words, partial pressure measured in atmospheres is always in atmospheres absolute, as are any other quantities in the models below.

Harabin et al's 1995 exponential model [39] (abbreviated H95A)

$$r(t) = a \cdot (PO_2 - thr)^b, \quad PO_2 > thr$$

$$= 0, \quad PO_2 \le thr$$

This model was published with parameters based on post-1970, pre-1993, immersed single- or multiple-depth exercise data with PO_2 from 1.6 to 2.5 atm.[39]

Parameters are

$a = 1.33 \times 10^{-3}\ \mathrm{min}^{-1}$
$b = 3.4$
$thr = 1$ atm.

Harabin et al's 1995 autocatalytic model [39] *(abbreviated H95B)*

The failure rate $r(t)$ is described as the build-up and break down of some quantity X, measured in atm, such that

$$\mathrm{d}X(t)/\mathrm{d}t = a \cdot PO_2 + k \cdot (PO_2 - P_{crit}) \cdot X(t), \text{ and}$$

$$r(t) = X(t) - thr,$$

where P_{crit} is the PO_2 above which X increases without bound, and both $r(t)$ and $X(t)$ have units of atm. This model, which includes recovery, is the one most often applied, e.g., in references 30 and 31.

The published parameters were based on post-1970, pre-1993, immersed single- or multiple-depth exercise data with PO_2 from 1.6 to 2.5 atm.[39]

Parameters are

$a = 6 \times 10^{-5}\ \mathrm{min}^{-1}$,
$P_{crit} = 2.04$ atm,
$thr = 8.74 \times 10^{-5}$ atm, and
$k = 0.66\ (\mathrm{atm} \cdot \mathrm{min})^{-1}$.

The value of *thr* is not 1 atm as tabulated in Reference 39, but was calculated as stated in reference 39 to be the steady-state value of X when $PO_2 = 1$ atm. This value gives results that correspond to those shown in the Reference. (In addition to the error in X, units of some of the parameters in the Reference are inconsistent and have been corrected here.)

Harabin et al's 1993 exponential model [9, 38] *(abbreviated H93)*

$$\begin{aligned} r(t) &= a \cdot b \cdot (PO_2 - thr)^{c} \cdot t^{b-1}, && PO_2 > \mathrm{thr} \\ &= 0, && PO_2 \leq \mathrm{thr} \end{aligned}$$

The published parameters used had been fitted based on all dive-stopping symptoms from post-1970, pre-1993, immersed, single-depth exercise data with PO_2 from 1.6 to 2.5 atm, including the first depth of the multi-depth exposures.[38]

Parameters are

$a = 2.9 \times 10^{-4}$
$b = 1.7$
$c = 3.6$
$thr = 1.3$ atm.

Arieli et al's 2002 models[40] *(abbreviated A02A, A02B)*

A cumulative oxygen toxicity index K,

$$K = t^{2} \cdot PO_2^{\,c}$$

was proposed. A symptom may develop if $K > K_c$, where K_c is a critical value.

The i th subject develops a symptom at time t_i, when exposed to PO_{2i} or

$$K_c = t_i^2 \cdot PO_{2i}^{\,c}.$$

$$\text{Hence, } \ln(t_i) = (c/2) \cdot \ln(PO_{2i}) + 0.5 \cdot \ln(K_c),$$

where ln is the natural logarithm. Although t_i can be censored, that is, the exposure can end before a subject develops symptoms, $\ln(t_i)$ follows a probability distribution where

$$\text{mean } \mu = (c/2) \cdot \ln(PO_2) + 0.5 \cdot \ln(K_c)$$

The authors assumed a Smallest Extreme Value distribution and used maximum likelihood methods to obtain parameters c, K_c, and standard deviation σ. They then calculated risk from the normal distribution

$$Z = [\ln(t) - \mu]/\sigma$$
$$\text{where } \mu = (c/2) \cdot \ln(PO_2) + 0.5 \cdot \ln(K_c).$$

Published parameters for the post-1970, pre-1993 single-depth exposure data (model A02A) where PO_2 ranges from 160 to 250 kPa were[40]

$c = 15.0$
$K_c = 5.28 \times 10^9$
$\sigma = 1.35$.

for PO_2 measured in atm (kPa/101.3), and time in minutes.

During periods of recovery, $K = K_0 \cdot e^{-0.079 \cdot t}$

Published parameters with an additional 2,039 closed-circuit oxygen training dives added to the previous data set (A02B) were[40]

$c = 6.8$
$K_c = 2.31 \times 10^8$
$\sigma = 2.02$.

MILD HYPEROXIA

The focus of this report is mild hyperoxia. Accordingly, all data where continuous exposure PO_2 was less than or equal to 1.7 atm were extracted from the record for further examination. Data from NEDU's development of decompression tables for the MK 16 Mod 1[30, 31] were explored in greater detail here, with the PO_2 overshoots initially ignored. The empirical probabilities of CNS oxygen toxicity events were calculated for combinations of PO_2 and exposure duration, as were confidence intervals on the estimates.

Calculation of probabilities

Only the two factors, PO_2 and exposure duration, were considered, but rest and exercise were examined separately. Water temperature and carbon dioxide retention could not be considered systematically for the data available. Dives were grouped by duration and "binned" into time increments unless statistical testing showed that two sets of data were from different probability distributions; Tarone's Z test[41] gave the probability that a single binomial distribution did not describe selected data sets.

When dive series were combined, probability of an event was calculated as total number of measured events, divided by total number of exposures across the group, and Agresti Coull 95% confidence intervals[42] were calculated. However, in the case of no measured events, Agresti Coull limits are very conservative. In that case the 95% confidence interval was calculated from the expression, $(1–p)^n = 0.05$, where n is the number of dives, and p is probability corresponding to the upper 95% confidence limit. The expression $(1–p)^n$ is the binomial probability of a series of n misses when the probability of a hit is p.

RESULTS

DATA SETS

The pre-1970 studies comprised 587 dry dives, 619 immersed resting dives, and 254 immersed exercise dives. The numbers of dive-stopping episodes were 318, 369, and 127, respectively. Dry PO_2 ranged from 1.3 to 3.6 atm, with durations from 6 to 180 minutes. PO_2 for immersed rest ranged from 1.8 to 3.9 atm, and durations ranged from 2 to 180 minutes. For immersed exercise, the range of PO_2 was from 1.5 to 2.5 atm, and durations ranged from 2 to 120 minutes.

The set of post-1970, pre-1993, immersed single- or multiple-depth exercise data with PO_2 from 1.6 to 2.5 atm as used by Harabin et al.[39] contained 688 records with 42 dive-stopping incidents of CNS oxygen toxicity from experiments in 21–22 °C (70–71 °F) water. The electronic version of the data set used here contains 689 records with 42 dive-stopping incidents. From the same sources, dive profiles that had been conducted in 13 °C (55 °F)[16] or 4 °C (34 °F) water were added,[13] six dives with no CNS incidents,[13] 25 dives with 3 dive-stopping incidents,[16] and 25 dives with 9 dive stopping events.[16]

When data collected since 1995 were included, the total number of dives with square PO_2 profiles and water temperature 21–29 °C (70–85 °F), that is, the post-1970 data described above plus the pulmonary oxygen toxicity studies, was 2657 dives with 57 dive-stopping episodes. (This count does not include the 56 dives and 12 dive-stopping occurrences at colder temperatures.) The total for all dives, warm and cold, including those with variable PO_2 profiles (decompression table testing) and the training dives, was 6,503 dives with 219 events. However, the outcomes for the training dives[37] follow a different probability distribution than the others — the value of Tarone's Z showed that the contribution of a second distribution was significant. The separate counts are 4,006 dives and 69 dive-stopping incidents for the experimental dives, and 2497 training dives with 150 reported incidents. The experimental dives include those for decompression table development, some of which were in 6 – 8 °C (43–46 °F) water,[34–36] and all of which involved PO_2 transients or drifts during dives. Most of the cold water decompression table development also included in-water oxygen accelerated decompression at 9 msw (29 fsw).[34, 35] The training dives included PO_2 from 1.3 to 1.4 atm known as a function of the average depth, and water temperatures of 16–28 °C (61–82 °F).

Mild Hyperoxia

The set of post-1970, pre-1993, immersed single- or first-depth exercise data with PO_2<1.7 atm contained 154 records from 21–22 °C (70–71 °F) water, with 2 dive-stopping incidents of CNS oxygen toxicity. Another 56 exposures in 13 °C (55 °F) or 4 °C (34 °F) water added 3 more dive-stopping incidents. Including more recent data, the total number of experimental dives with PO_2 <1.7 atm and square PO_2 was 1173 exposures with 7 dive-stopping episodes. The decompression table development dives brought the total to 3,454 dives (not including the training dives) with 7 dive-stopping incidents, an overall probability of 0.2%. In the 2497 training dives there were 150 incidents, as is stated above, an overall probability of 6.0%.

MODELS COMPARED TO THEIR CALIBRATION DATA

Models H95A, H95B

The 1995 models correspond very well in aggregate to the data from which they were fitted (as published, 43 incidents vs. 42 measured,[39] probability 6.3% calculated vs. 6.1% measured). However, they perform considerably less well for specific conditions within that data set (Figure 1).

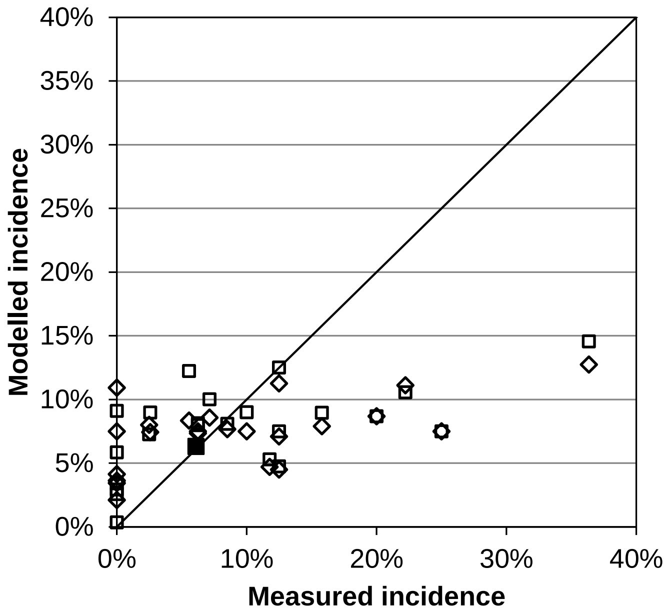


Figure 1. Probability of dive-stopping events, models H95A and H95B applied to their calibration data. The identity line is shown for comparison. □: H95A. ◊: H95B. ■: total (aggregate) for both models. Numbers were taken from Table 3 in ref 20.

Figure 1 shows probabilities of dive-stopping events predicted by models H95A and H95B, plotted against measured probabilities (number of incidents per number of dives) for each dive profile used. The correlations, model to experiment, are 0.58 and 0.56 for models H95A and H95B, respectively. Correspondence is good only for profiles with approximately 8% probability of dive-stopping events. When the measured incidence is lower, the models overestimate the risk, and when it is higher, they underestimate it. The best fit lines for H95A and H95B predictions as functions of measured probability have intercepts at 6%. The slope is 0.21 for H95A and 0.16 for H95B. If the intercept is forced to be zero, the slopes become 0.51 and 0.47 for Models H95A and H95B, respectively.

Model H93

Model H93 also agrees very well with its calibration data set in total number of incidents predicted and observed: 20 predicted, 24 observed. Once again, though, the correspondence is poor on a per profile basis, as is shown in Figure 2. The correlation between predicted and measured number of events is 0.48, and low risk tends to be overestimated by the model, while higher risk is underestimated. The best fit line for predicted probability as a function of measured probability has an intercept at 2% and a slope of 0.39. If the line is forced through zero, the slope is 0.56.

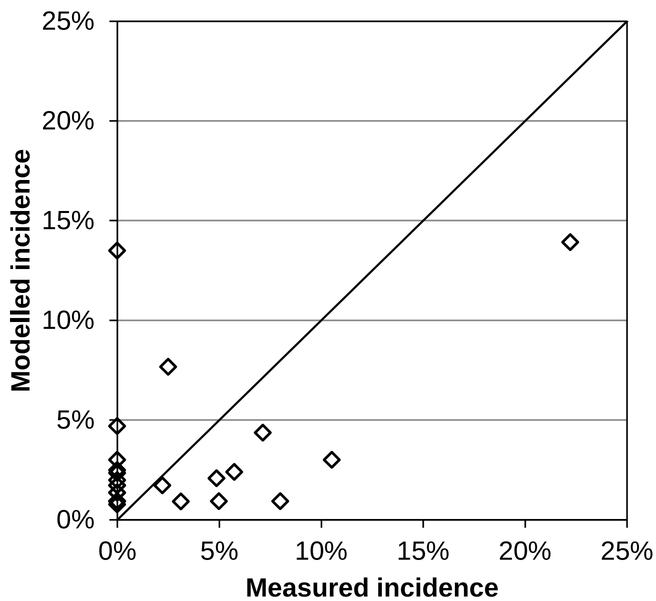


Figure 2. Probability of dive-stopping events, models H93 applied to its calibration data. Only the first depths of multi-depth profiles were used. The identity line is shown for comparison.

<u>Models A02A, A02B</u>

Model A02A predicts 23 events to the 24 observed in its calibration set, while Model A02B predicts 148 to the 174 observed. Risk is overestimated for zero measured incidence and underestimated for the highest measured incidence, but is broadly correct in the mid range (Figure 3). The best fit lines for predicted probability as a function of measured probability have intercepts and slopes of 3% and 0.17 for A02A and 4% and 0.12 for A02B. When the lines are forced through the origin, the slopes become 0.35 and 0.40 for Models A02A and A02B, respectively.

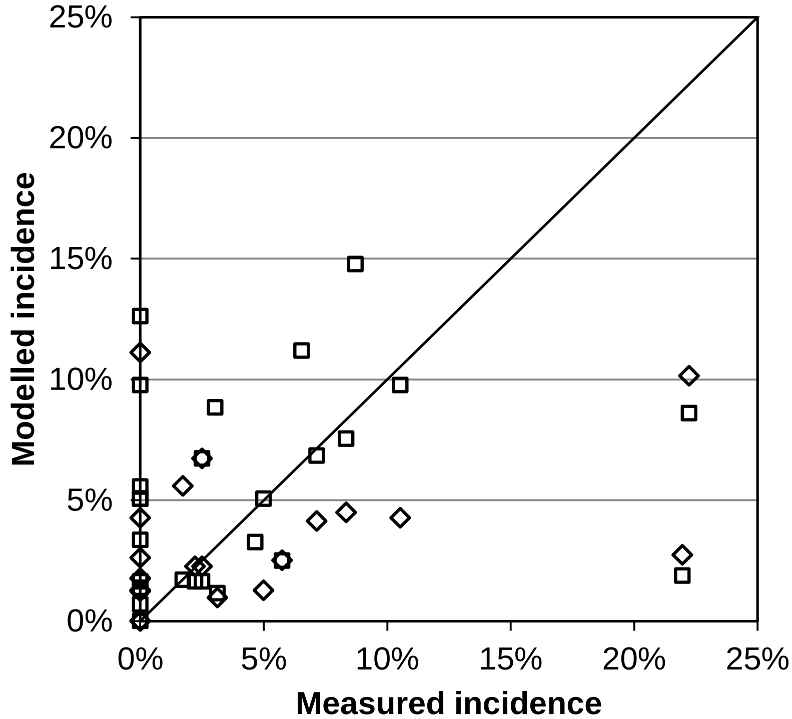


Figure 3. Probability of dive-stopping events, models A02A, A02B applied to their calibration data. □: A02A. ◊: A02B.Only the first depths of multi-depth profiles were used. The identity line is shown for comparison.

MODELS APPLIED TO OTHER SUBSETS OF DATA

Dry resting data[2–7 summarized in 1]

None of the predictive models for CNS oxygen toxicity had been calibrated for dry chamber data. Because hyperbaric oxygen exposure dry and immersed have different CNS effects,[9] poor model performance was expected. The surprise in Figure 4 is that model predictions based on immersed data often underestimated the risk of CNS oxygen toxicity in the dry. Correlations are 0.47, 0.49, 0.41, 0.51, and 0.48 for Models H95A, H95B, H93, A02A, and A02B, respectively.

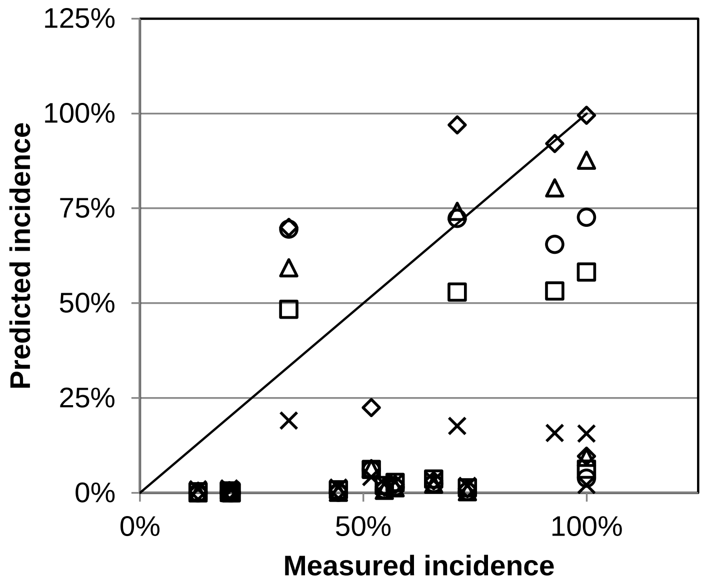
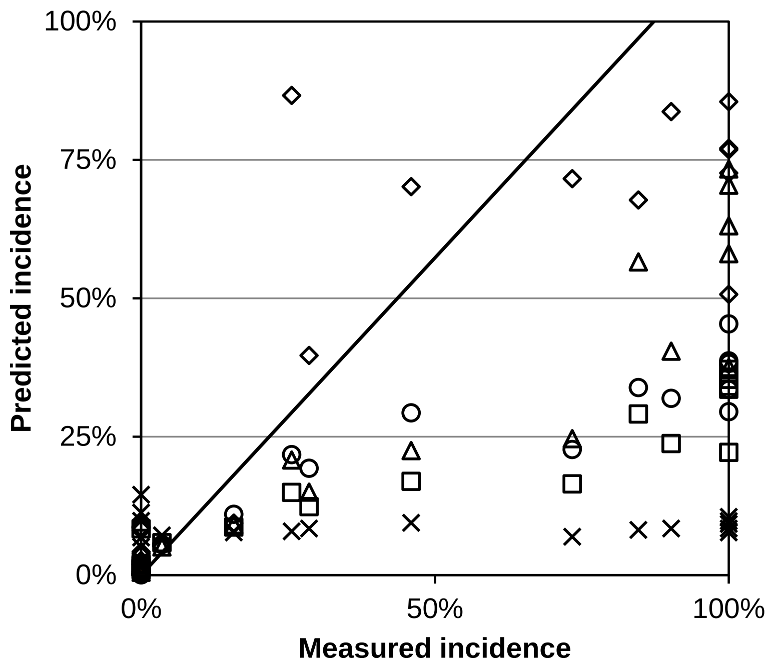


Figure 4. Probability of dive-stopping events during dry hyperbaric exposure, model prediction vs. measured data. □:H95A. ◊:H95B, ○:H93, Δ:A02A, X:A02B. The identity line is shown.

Immersed resting data [4, 6 (from 1), 19–25]

The models were not constructed to predict CNS oxygen toxicity for immersed resting data. As evident in Figure 5, models based on immersed exercise data from after 1970 underestimate the risk of CNS oxygen toxicity from resting exposures when measured risk is high (pre-1970 data with high PO_2, Fig. 5a), but overestimate it when risk is low (post-1985 data, Fig. 5b).

a



b

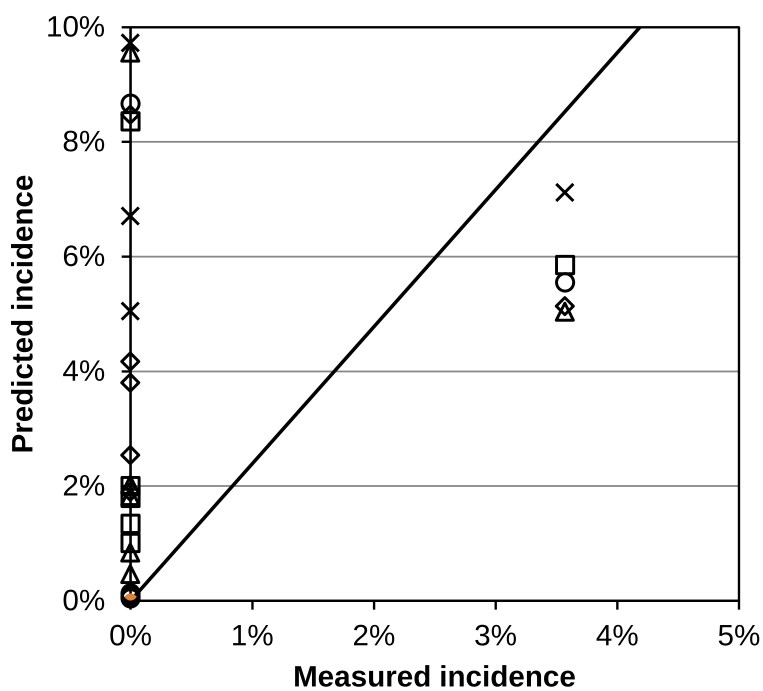


Figure 5. Probability of dive-stopping events during immersed, resting hyperbaric exposure, model prediction vs. measured data. □:H95A. ◊:H95B, O:H93, Δ:A02A, X:A02B. The identity line is shown. a) all data. b) an enlargement of the lower left quadrant with the identity line retained.

Immersed exercise data before 1970 [4, 10, 11 (from 1)]

The models seriously underestimate the risk for immersed exercise reported between 1945 and 1949, as shown in Figure 6.

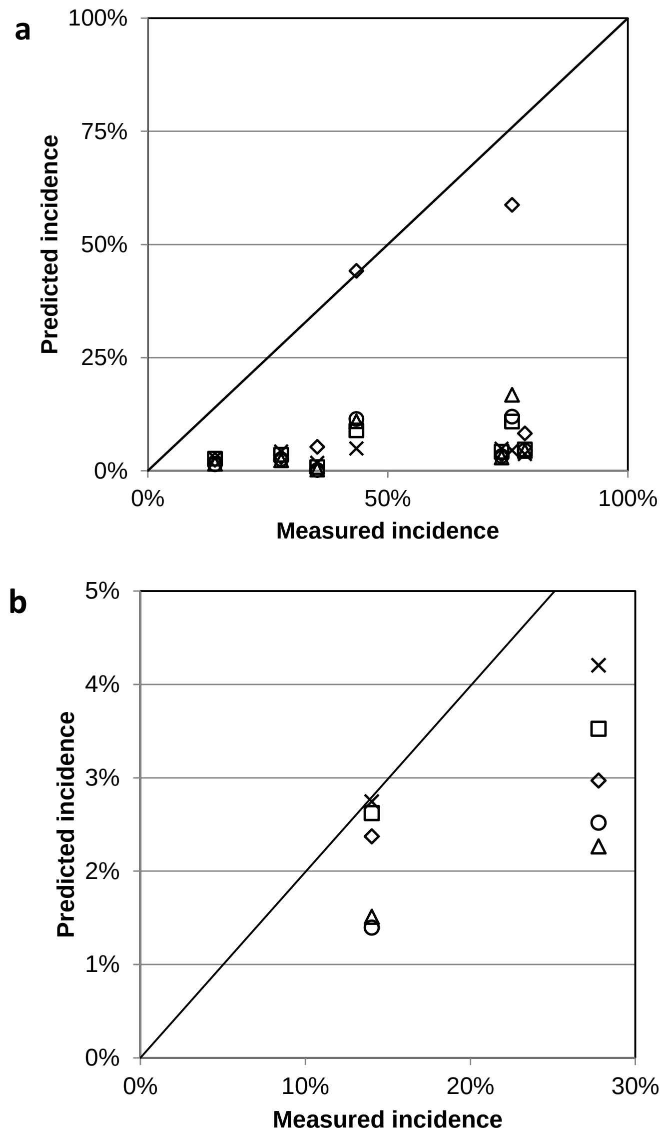


Figure 6. Probability of dive-stopping events during immersed, hyperbaric exposure with arm-cranking exercise, model prediction vs. measured data. □:H95A. ◊:H95B, O:H93, Δ:A02A, X:A02B. The identity line is shown. a) all data. b) an enlargement of the lower left quadrant with identity line retained.

Immersed leg exercise data since 1970[12–17, 26–37]

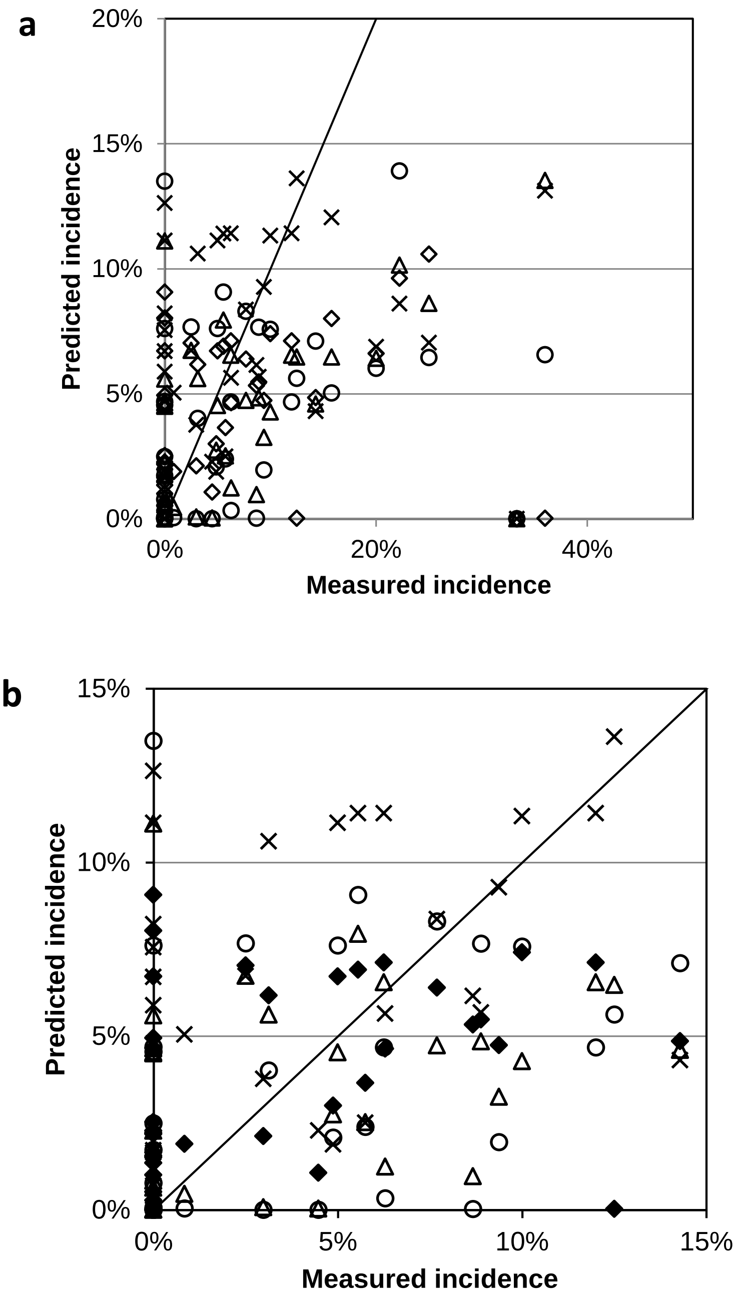


Figure 7. Probability of dive-stopping events during immersed, hyperbaric exposure with leg ergometer exercise, model prediction vs. measured data. □:H95A. ◊:H95B, O:H93, Δ:A02A, X:A02B. The identity line is shown. a) all data. b) an enlargement of the lower left quadrant. In panel b, the symbols for H95B are shown filled for emphasis.

When the models are applied to leg ergometer exercise, the data for which they were developed, they underestimate high risk (Figure 7a), seriously overestimate low risk — note the scatter up the y-axis of Figure 7 — and yield estimates that are evenly scattered on both sides of the identity line for exposures with measured risk between about 3 and 10%. Model H95B is emphasized in Figure 7b because it is commonly applied to obtain CNS oxygen toxicity risk estimates.

Figure 7 is primarily a composite of Figures 1–3, although some newer data[26–37] are included, and the multi-depth exposures are considered for all models. Many experimental data acquired since 1995 have no measured incidence of CNS oxygen toxicity. They contribute to the “smearing” on the y-axis.

DATA WITH $PO_2 \leq 1.7$ ATM

Exercise data from studies before 1970[10, 11] or dry[7]

Data from early studies with arm rather than leg exercise showed a high incidence of CNS oxygen toxicity. They are presented in Table 1 for completeness, but are not used further in this report.

Table 1.
Reported incidence of CNS oxygen toxicity before 1970, mildly hyperoxic

PO_2 (atm)	Duration (minutes)	Number of dives	Incidence of CNS oxygen toxicity (95% CI)		
			Dive stopping	Definite	Any
Immersed, arm exercise					
1.3[10]	75	12	8.3% (0-41%)	8.3% (0-41%)	8.3% (0-41%)
1.5[10]	86	17	17.6% (3.6–44%)	29% (10.9–56%)	29% (10.9–56%)
1.4[11]	113	10	0% (0–26%)	0% (0–26%)	0% (0–26%)
1.6[11]	81	5	0% (0-58%)	0% (0-58%)	0% (0-58%)
Dry exercise[7]					
1.3	40	44	2.3% (0–13.4%)	20.5% (10–35%)	20.5% (10.5–35.3%)
1.4	40	47	6.4% (1.3–18%)	12.8% (5.3–26%)	12.8% (5–26%)
1.5	40	45	2.2% (0–13%)	20.0% (10–35%)	20.0% (10–35%)
1.6	40	45	2.2% (0–13%)	44.4% (30–59%)	44.4% (30–59%)
1.7	40	49	6.1% (1.2–18%)	73.5% (59–84%)	73.5% (59–84%)

Superscripts are reference citations.

Immersed resting exposures

Data from resting, immersed exposures are restricted to two PO_2 values, 1.4 and 1.6 atm.[19–25, 33] No dive-stopping or definite incidents of CNS oxygen toxicity were reported (Table 2), but some probable incidents occurred, specifically, post dive irritability after pairs of 180 min[22] and single 480 min[24] dives, and vertigo and later sleep disturbance after 360 min dives.[22] The data from the right-most column are graphed in Figure 8a.

Table 2.
Reported incidence of CNS oxygen toxicity, immersed at rest, mildly hyperoxic

PO_2 (atm)	Duration (minutes)	Number of dives	Incidence of CNS oxygen toxicity (95% CI)		
			Dive stopping	Definite	Any
1.4 [22]	180	144	0% (0 – 2.1%)	0% (0 – 2.1%)	1.4% (0.1 – 5.4%)
1.4 [19, 20, 23]	240	280	0% (0 – 1.1%)	0% (0 – 1.1%)	0% (0 – 1.1%)
1.4 [19, 22]	360	259	0% (0 – 1.1%)	0% (0 – 1.1%)	0.4% (0 – 2.3%)
1.4 [19, 21, 24]	480	79	0% (0 – 3.7%)	0% (0 – 3.7%)	2.5% (0.1 – 9.5%)
1.4 [22]	360 (split)	24	0% (0–11.7%)	0% (0–11.7%)	8.3% (0.2–28.1%)
1.6 [25]	360	34	0% (0–8.4%)	0% (0–8.4%)	2.9% (0–17%)
1.6 [33]	60	12	0% (0–22%)	0% (0–22%)	0% (0–22%)

Superscripts are reference citations.

Immersed exposures with exercise since 1970

Experimental data are presented in Table 3, and those from training dives in Table 4. The probability of any CNS oxygen toxicity symptom is shown in Figure 8b.

Symptoms possibly caused by CNS oxygen toxicity were reported after a few of the NEDU exercise dives with PO_2 = 1.4 atm. One caused a dive to be aborted: early in a 180-minute dive, one diver experienced deltoid muscle twitches and left the water.[28] At the end of 240-minute dives, one diver reported tingling of the head, four divers reported irritability, and one reported disturbed sleep the night after a second 240-minute dive following a 15-hour surface interval.[26] One diver reported twitching of his bicep after 120 minutes of diving but completed the 240-minute dive.[26]

Probable CNS oxygen toxicity symptoms, some of which were dive-stopping, were reported during the dives with PO_2 = 1.6 atm, the first depth of several multi-depth profiles.[16,17] One diver reported numbness, tingling, poor concentration and dizziness after only 5 minutes. One diver reported tinnitus and nausea beginning in the first 20 to 30 minutes of two separate dives, but he completed both dives. One diver experienced nausea and tingling after 147 minutes, and another, nausea after 235 minutes. One diver stopped because of nausea after 92 minutes, and another stopped because of nausea and dizziness after 99 minutes.

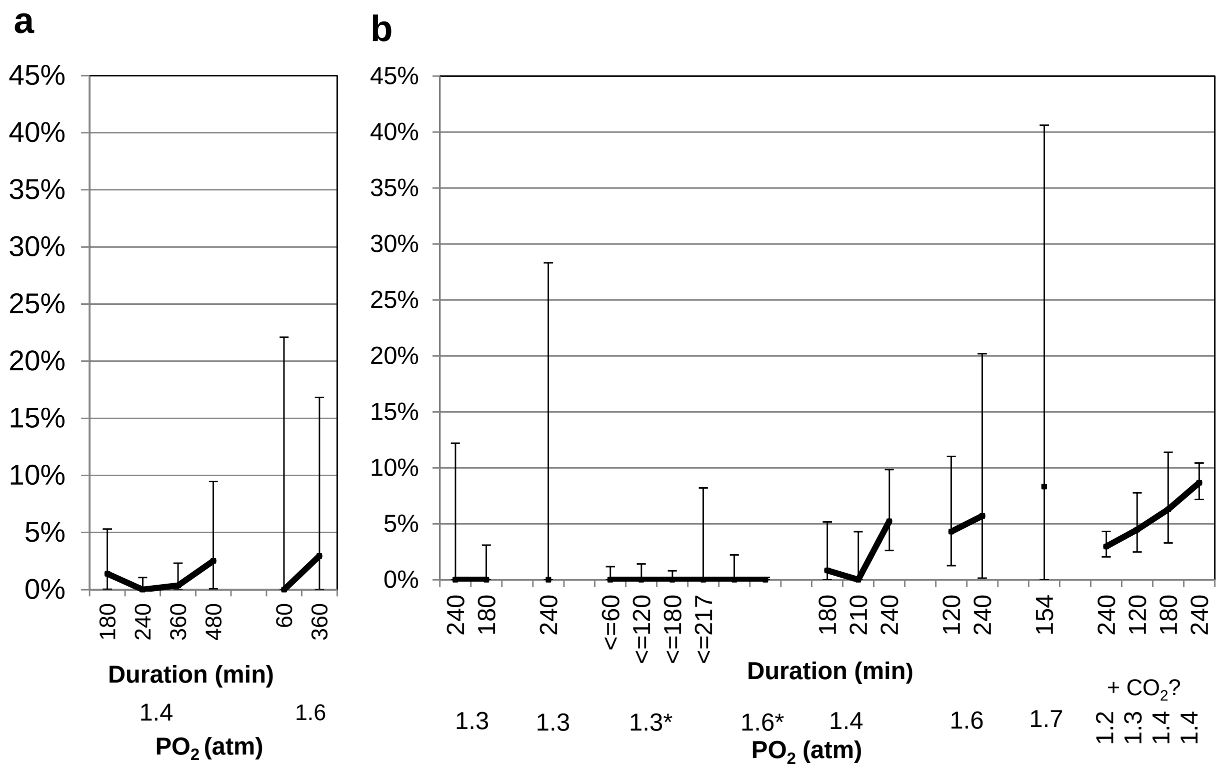


Figure 8. Measured incidence of any symptoms of CNS oxygen toxicity for exposures to PO_2 ≤1.7 atm, with 95% confidence intervals, a) immersed rest, and b) immersed leg exercise. Related experiments are joined by solid lines.
* indicates decompression table development dives binned by duration of hyperoxic exposure (dive plus decompression). The nominal PO_2 is listed for those dives, but overshoots led to higher PO_2 for the initial phases of each dive. Divers exercised on the bottom during the dive time but rested during decompression. The right-most two points of the dives marked * are DERA[36] and DCIEM[34–35] dives (max PO_2 = 1.6 atm) as summarized in Reference 31.
"+CO_2?" labels training dives in which inspired CO_2 is suspected. (See "DISCUSSION, DATA SET DIFFERENCES, *Dive Conditions*, UBA, Inspired CO_2, and Work of Breathing.")

Table 3.
Reported incidence of CNS oxygen toxicity, immersed, leg exercise, mildly hyperoxic, since 1970

PO_2 (atm)	Duration (min)	Number of dives	Incidence of CNS oxygen toxicity (95% CI)		
			Dive stopping	Definite	Any
1.3[28]	180	95	0% (0–3.1%)	0% (0–3.1%)	0% (0–3.1%)
1.3[28]	240	23	0% (0–12%)	0% (0–12%)	0% (0–12%)
1.3[12]	240	9	0% (0–28%)	0% (0–28%)	0% (0–28%)
1.3[30, 31] *	≤60	254	0% (0–1.2%)	0% (0–1.2%)	0% (0–1.2%)
1.3[30, 31] *	≤120	209	0% (0–1.4%)	0% (0–1.4%)	0% (0–1.4%)
1.3[30, 31] *	≤180	372	0% (0–0.8%)	0% (0–0.8%)	0% (0–0.8%)
1.3[30, 31] *	≤217	35	0% (0–8.2%)	0% (0–8.2%)	0% (0–8.2%)
1.3 [32] *	≤416	89	0% (0–3.3%)	0% (0–3.3%)	0% (0–3.3%)
1.3 [36 in 31]*		133	0% (0–2.2%)	0% (0–2.2%)	0% (0–2.2%)
1.6 [34, 35 in 31] *		1343	0% (0–0.2%)	0% (0–0.2%)	0% (0–0.2%)
1.4[27,28]	180	119	0.8% (0–5.2%)	0% (0–2.5%)	0.8% (0–5.2%)
1.4[29]	210	68	0% (0–4.3%)	0% (0–4.3%)	0% (0–4.3%)
1.4[26]	240	172	0% (0–1.7%)	0% (0–1.7%)	5.2% (2.6–9.9%)
1.6[16,17]	120	93	2.2% (1–8.2%)	0% (0–3.2%)	2.2% (1–8.2%)
1.6[16]	240	35	5.7% (0.2–20%)	0% (0–8.2%)	5.7% (0.2–20%)
1.6[16,17] cold	120	25	8% (0.3–27%)	0% (0–11%)	8% (0.3–27%)
1.6[16] cold	240	25	12% (2.4–32%)	0% (0-11%)	12% (2.4–32%)
1.7[13]	154	12	8.3% (0–41%)	0% (0–22%)	8.3% (0–41%)
1.7[13] cold	163	6	0% (0–39%)	0% (0–39%)	0% (0–39%)

The dives with PO_2 = 1.6 atm are the first depths of multi-depth profiles.
*Dives from references 30–36 are listed by nominal PO_2, but all dives included PO_2 overshoots on descent, and those listed with PO_2 = 1.6 atm (nominal maximum PO_2) also included in-water oxygen accelerated decompression at 9 msw (29 fsw). Data from references 34–36 were obtained from summaries in Reference 31.

No diver reported any symptoms of CNS oxygen toxicity during or after a dive conducted to establish decompression tables despite the overshoot of PO_2 beyond the set points. This was true for the 805 dives for the MK 16 Mod 1 on N_2O_2[30] and on HeO_2,[31] for the 1343 manned dives with the CUMA which included a decompression stop with 100% oxygen at 9 msw,[34,35 from 31] and for the 133 dives with the CDBA.[36]

The predictions of each of the five models for the experimental dives with square PO_2 profiles at mild hypoxia data are given in Table 4. The predictions are within the 95% CI for the measurements (Table 3) only because confidence bands are very wide. Note the trend for models to overestimate the mildly hyperoxic data, except for those from cold dives.

Table 4.
Measured and predicted incidence of dive-stopping CNS symptoms, square PO_2 profile, mildly hyperoxic

PO_2 (atm)	Duration (min)	Number of dives	Measured Dive stopping (from Table 3)	Predicted Incidence of CNS dive-stopping oxygen toxicity				
				H95A	H95B	H93	A02A	A02B
1.3[28]	180	97	0%	0.1%	0.7%	0%	0%	0%
1.3[28]	240	23	0%	0.1%	0.9%	0%	0%	0%
1.4[27]	180	119	0.8%	1.0%	1.9%	0%	0.5%	5.0%
1.4[29]	210	68	0%	1.2%	2.2%	0.1%	0.6%	5.9%
1.4[26]	240	159	0%	1.3%	2.5%	0.1%	0.8%	6.7%
1.6[16, 17]	120	93	2.2%	2.4%	2.5%	0.9%	1.3%	5.1%
1.6[16]	240	35	5.7%	4.7%	5.0%	3.0%	4.3%	9.8%
1.6[16] cold	120	25	8%	2.4%	2.5%	0.9%	1.3%	5.1%
1.6[16] cold	240	25	12%	4.7%	5.0%	3.0%	4.3%	9.8%
1.7[13]	154	12	8.3%	5.1%	4.6%	4.7%	4.5%	7.6%
1.7[13] cold	163	6	0%	5.4%	4.9%	4.6%	4.6%	8.2%

The dives with PO_2 = 1.6 atm are the first depths of multi-depth profiles.
Superscripts are reference citations.

The incidence of CNS oxygen toxicity reported from training dives (Table 5) is much higher than that from the other dives reported here. The only model that approaches the high incidence from these dives is A02B, which used these data as part of its calibration set. Reported events from the training dives were not categorized as dive stopping or not, nor as probable or definite.

Table 5.
Probability of CNS oxygen toxicity, training dive data, mildy hyperoxic.[37] Model predictions are included.

PO_2 (atm)	Duration (min)	Number of dives	Cumulative incidence of CNS oxygen toxicity (95% CI)					
			Measured[37]	H95A	H95B	H93	A02A	A02B
1.2	60	905	1.9% (1.2–3.0%)	0%	0.2%	0%	0%	6.2%
1.2	120		2.4% (1.6–3.7%)	0%	0.4%	0%	0.1%	15.0%
1.2	180		2.8% (1.9–4.1%)	0.1%	0.6%	0%	0.2%	24.2%
1.2	240		3.0% (2.0–4.3%)	0.1%	0.9%	0%	0.4%	33.1%
1.3	60	268	3.7% (2.0 –6.9%)	0.1%	0.3%	0%	0%	1.0%
1.3	120		4.7% (2.6 – 8.1%)	0.2%	0.7%	0%	0%	2.3%
1.4	60	1185	2.2% (1.5–3.2%)	0.2%	0.5%	0%	0%	1.3%
1.4	120		3.5% (2.6–4.7%)	0.5%	1.1%	0%	0.1%	3.0%
1.4	180		5.7% (4.5–7.1%)	0.7%	1.6%	0%	0.3%	4.6%
1.4	240		8.5% (7.1–10.3%)	1.0%	2.2%	0%	0.6%	6.2%
1.5	60	159	3.8% (1.5–8.3%)	0.5%	0.7%	0%	0.1%	1.7%
1.5	120		5.0% (2.4–9.9%)	1.0%	1.5%	0.1%	0.4%	3.8%
1.5	180		6.3% (3.3–11.4%)	1.5%	2.3%	0.2%	0.8%	5.7%

The information of Table 3 for different dive series with square PO_2 profiles is further condensed in Table 6. Here, dive series with similar PO_2 and dive durations have been combined, and the first part of longer dives was used to give information about shorter dives, increasing the numbers of dives and thus the precision of estimates. Assuming that what is a safe exposure at higher PO_2 is also safe at lower PO_2, the information from PO_2 = 1.4 atm can replace the somewhat sparser set at PO_2 = 1.3 atm. Similar information for resting exposures (Table 2) is presented in Table 7.

Table 6.
Composite probabilities of CNS oxygen toxicity at mild hyperoxia and moderate exercise, by PO_2 and duration. Upper 95% confidence limit

PO_2 (atm)	Duration (min)	Probability of CNS oxygen toxicity event		
		Dive stopping	Definite	Any
≤1.4	≤180	≤1.8%	≤0.83%	≤1.8%
≤1.4	≤210	≤1.2%	≤1.2%	≤5%
≤1.4	≤240	≤1.7%	≤1.7%	≤9.8%
1.6	≤120	≤8.1%	≤3.2%	≤11%
1.6	≤240	≤20.2%	≤8.2%	≤20.2%
1.7	≤154	≤41%	≤22%	≤41%

Table 7.
Composite probabilities of CNS oxygen toxicity at mild hyperoxia and rest. Upper 95% confidence limit

PO_2 (atm)	Duration (minutes)	Probability of CNS oxygen toxicity event		
		Dive stopping	Definite	Any
≤1.4	≤180	≤0.38%	≤0.38%	≤1.0%
≤1.4	≤240	≤0.48%	≤0.48%	≤0.48%
≤1.4	≤360	≤0.86%	≤0.86%	≤1.8%
≤1.4	≤480	≤3.87%	≤3.87%	≤9.5%
1.6	≤60	≤ 6.3%	≤ 6.3%	≤ 6.3%
1.6	≤360	≤8.4%	≤8.4%	≤17%

DISCUSSION

DATA SET DIFFERENCES

The data group broadly into four subsets: dry studies, pre-1970 immersed experiments, post-1970 experimental data, and post-1970 training dives. A major difference between pre- and post-1970 studies was the severity of exposure; the older experiments were frequently at high PO_2 for long durations. However, differences in incidence of suspected or definite CNS oxygen toxicity are seen even when similar exposures are compared. Harabin[9] thoroughly discussed the differences between immersed and dry or pre- and post-1970 studies and concluded that an important difference between "old" and "new" immersed exercise studies was that between arm and leg exercise. Neither dry studies nor pre-1970 immersed data are discussed further here.

The experimental and training data during mild hyperoxia have very different incidences of apparent CNS oxygen toxicity (Tables 3 and 4, Figure 8b). Possible reasons are differences in definition and reporting of suspected CNS oxygen toxicity, and differences in dive conditions.

Reporting

For the experimental dives designed to study CNS oxygen toxicity, symptoms were expressed as definite, probable, or convulsion,[15–17] but were coded as dive stopping or not dive stopping.[1] (Not all definite symptoms caused a dive to terminate, and not all dive-stopping symptoms were definitely CNS oxygen toxicity.) Only symptoms that were predetermined to be characteristic of CNS oxygen toxicity were considered, and divers were instructed to complete the protocol unless they felt the need to report symptoms.[16] During the dives to test decompression profiles,[30, 31] divers were asked simply to report anything out of the ordinary. This would tend to minimize reports of symptoms perceived to be ordinary annoyances of diving or even of oxygen diving. In contrast, during dives designed to study pulmonary oxygen toxicity, the dive side asked about classic symptoms of CNS oxygen toxicity, and divers filled out a questionnaire after the dives.[19–29] After training dives, divers completed an anonymous questionnaire.[37] However, although some symptoms on the list may have otherwise gone unreported, for example, irritability or muscle twitching after the pulmonary function dives,[22, 24, 26, 28] the symptoms considered to be CNS oxygen toxicity during the training dives--nausea, dizziness, tinnitus, disorientation, tingling in the limbs, hearing disturbance, loss of consciousness, visual disturbances, vomiting, anxiety, facial twitching, change in taste or smell, non-cold shivering, confusion, and amnesia[37] – are unlikely to have been otherwise ignored as being “normal after diving”. It is significant to note, though, that of the 2527 training dives very few of the 150 episodes that were deemed to be CNS oxygen toxicity appear to have resulted in early termination of a dive: in a separate report[43] the authors mention 2522 uninterrupted dives from this series. However, the 0.38% incidence of loss of consciousness cannot be ignored. [37]

Dive Conditions

Exercise modality, intensity, and duration.

Exercise protocols differed across data sets. During experimental dives, one study at PO_2 = 1.3 atm (Table 3) involved continuous swimming against a trapeze to keep a weight suspended,[13] and one conducted to test decompression tables, also at PO_2 = 1.3 atm (Table 3), had divers lifting weights on the bottom.[32] For the other studies, exercise was imposed using submerged cycle ergometers. At PO_2 = 1.6 atm[16, 17] (Table 3), divers cycled at 50 W (equivalent to about 110 W in the dry[44]), alternating 6 minutes of work and 4 minutes of rest, in an effort to establish a rate of oxygen uptake of approximately 1.3 $L \cdot min^{-1}$.[16] For the studies with PO_2 = 1.3 or 1.4 atm designed to study pulmonary oxygen toxicity[26–29] (Table 3), work cycles were 30 minutes on, 30 minutes off. Ergometers were set initially to 50 W, but power output was adjusted to keep heart rate between 100 and 110 beats per minute.[26] For the studies at PO_2 = 1.7 atm[13] (Table 3), cycles were 6 minutes at work, 4 minutes at rest, for some (six warm, six cold dives) with the ergometer set to 50 W, and for the other six dives, with ergometer loads increasing progressively from 25 to 150 W in steps of 25 W. For the development and testing of decompression tables with PO_2 = 1.3 atm[30, 31] (Table 3), the work cycle on the bottom was 5 minutes on, 5 minutes off, with ergometer settings of 35 to 50 W (equivalent to approximately 95 to 110 Watts in air[44]). For other decompression table development, [33–35] work cycles were 5 minutes on, 5 minutes off at nominally 50 W. However, during training dives[37] (Table 4), divers swam in the open ocean where the time-averaged rate of oxygen uptake was measured at 1.4 $L \cdot min^{-1}$ in a group of 8 divers.[45] Power output in those dives was probably variable, depending on currents, relative swimming speed of buddy pairs, swimming efficiency, level of enthusiasm for the task, and experience, among other factors. Indeed, prolonged periods of strenuous activity with high CO_2 production were implicated in scrubber failure in some dives.[43]

Increased metabolic rate has been shown to decrease latency to CNS oxygen toxicity.[46] The exercise dives involving decompression[30, 31, 33–36] thus would be expected to have lower risk than the other experimental dives, since they involved exercise only on the bottom, and bottom times were most commonly shorter than 60 min; only 11% of the 959 N_2O_2 or HeO_2 MK 16 dives[30-32] included bottom times of 90 minutes or longer. Rest during decompression often comprised significant fractions of the dives. Although the average energy output during the other experimental dives was nominally similar to that during training dives, experimental dives had constant exercise duty cycles, while training dives may have included bursts of much higher activity.

Temperature

Water temperatures were controlled to be comfortably warm for swim-suited divers during the dives designed to study pulmonary oxygen toxicity at PO_2 = 1.3 and 1.4 atm.[26–28] During the PO_2 =1.6 atm dives, the goal was to have a reduction of core temperature of 0.25 °C per hour, and divers wore “shorty” wetsuits in the 21–22 °C (70–71 °F) water, or full ¼” neoprene for the 13°C (55°F) water.[16] During the MK 16 Mod 1 decompression table dives the goal was to keep the divers comfortable, and divers wore wet suits.[30, 31] For the CUMA decompression table development divers wore dry suits in the 6–8 °C (44–46 °F) water.[33–35] During the training dives, water temperature varied by season. With wet suits and water temperature 17–18.5 °C, core temperature in 8 divers dropped about 0.5 °C per hour,[45] but no significant effect of water temperature on the prevalence of CNS oxygen toxicity symptoms was seen within the training dive data.[37]

Because of the differences in thermal protection and in thermal conditions, temperature cannot be assessed as a source of difference across data sets. Table 3 shows that in the very small dive series with two water temperatures and PO_2 = 1.7 atm, no subject experienced symptoms at either temperature,[13] while in the slightly larger series with two temperatures and PO_2 = 1.6 atm, apparent incidence was higher in cold water despite thermal protection.[16,17]

UBA, Inspired CO_2, and Work of Breathing

CO_2 retention is a well-known contributor to CNS oxygen toxicity, and inhaled CO_2 is thus a risk factor. For the dives at PO_2 = 1.4 atm, divers breathed humidified 100% oxygen open circuit with the MK 20 UBA, that is, with an AGA mask and demand regulator,[26–28] with no risk of inspired CO_2. For the dives with PO_2 = 1.6 atm, divers breathed the LAR V rebreather, and sampling confirmed absence of CO_2 in the inspired gas.[15 – 17] Similarly, during dives to test decompression tables, inspiratory gas in the MK 16 Mod 1[30, 31] and the CUMA rig[33–35] was monitored to ensure no appreciable inspired CO_2. Most training dives were conducted using the Oxygers 57, and some with the OxyNG 2 (Ran Arieli, personal communication).

Inspired gas monitoring was impossible during open-water training dives, but elevated inspired CO_2 was found to be a problem in at least some similar dives: in 18 training dives aborted for symptoms of CNS oxygen toxicity (dives apparently not included in the training dive data set), the UBA was tested with exercise after the abort, and inspired CO_2 exceeded 2.5 kPa in eleven of the UBAs.[43] Further, a study of CO_2 absorbent canister duration of the two UBAs,[47] initiated because of the elevated CO_2 mentioned above, measured canister breakthrough near the rated 3- and 4-hour endurance time[48] for the Oxygers 57/97 (or Oxygers 1957) and the OxyNG, respectively with very low CO_2 flow (0.95 $L \cdot min^{-1}$), and less with moderately low CO_2 flow (1.12 $L \cdot min^{-1}$). Indeed, the French Navy has reported 26 cases of hypercapnia because of scrubber failure in divers using the Oxygers 57 and other UBAs, and has noted a decrease in cases of hypercapnia and of hyperoxic seizures since a UBA with longer scrubber duration has been introduced.[49] Inspired CO_2 in rats, and probably also in humans, can cause CNS oxygen toxicity at a PO_2 where symptoms would not otherwise occur,[50] and hypercapnia alone can cause impairment or loss of consciousness during training dives.[49] Inspired CO_2 is an important difference between the experimental and training dive data. The training data should probably be considered to show effects of CO_2 during mild hyperoxia.

External breathing resistance diminishes the normal increase in minute ventilation during exercise[51], causing CO_2 retention even in the absence of CO_2 in inspired gas. Of the dive series under consideration, only the deep N_2O_2 dives with the MK 16 or CUMA will have included increased internal work of breathing. However, work of breathing of the MK 20, LAR V, MK 25, MK 16, CUMA, Oxygers 57 and OxyNG2 may differ. Some may be particularly sensitive to diver body orientation in the water, and some may become hard to breathe with increased flow requirements of exercise. A UBA that is hard to breathe will cause CO_2 retention regardless of the performance of the scrubber: CO_2 retention related to heavy exercise with a rebreather has been identified as the cause of 36 rebreather accidents in the French Navy.[49]

MODEL PREDICTIONS

All Data

Prediction of CNS oxygen toxicity is far from precise. Rare events are very difficult to model, and particularly so if all the variables are not clear. The published models predict the correct number of incidents of CNS oxygen toxicity for their calibration sets, but they do not distribute the episodes correctly across exposure conditions even for the calibration data (Figs. 1–3). Performance on a dive-by-dive basis is even worse when data outside the calibration sets are included (Fig. 7). At low incidence, the model predictions are particularly wild (y axis, Figure 7).

The calibration data for all of the published models involved PO_2 that was a function of depth and that changed in large “square” steps. Thus, the modeling process could not differentiate between instantaneous PO_2 and integrated PO_2 over some time period. Mechanistically, an integral of PO_2 with some “memory” period may be more important for the dynamics of initial vasoconstriction and subsequent cerebral vasodilation, a dynamic process driven in part by nitric oxide (NO) depletion by oxygen radicals and subsequent increased production using oxygen as a substrate.[52] A concept of integrated rather than instantaneous PO_2 makes more comprehensible the convulsions that Butler reported at 20 fsw after excursions to 40 fsw.[17]

The models accumulate risk from prior exposure but do not (and cannot) consider other possible changes caused by immediate history, e.g., sensitization or protection caused by prior hyperoxic exposure. For lack of data, the models ignore both metabolic rate (kept constant during the dives used to construct the models) and CO_2. Unfortunately, any dive where metabolic rate does not match that of the calibration data, for example, the resting or exercise data from before 1970 (Figs.5 and 6) or any dive with non-square PO_2 profiles, is outside the range of the models.

Mild Hyperoxia

The poor fit of the models to data for mild hyperoxia, even for controlled metabolic rate, and single, constant PO_2 is evident in Table 5. Model H95B, Harabin’s autocatalytic model, overestimates all but the data from PO_2 = 1.6 atm. Model H93 has a threshold of 1.3 atm.

The limitation of model H95B when presented with PO_2 transients is evident from the dives conducted with rebreather UBAs that control oxygen partial pressure independent of depth.[30–36] (The other models examined here would not be expected to perform any better.) The UBAs cannot eliminate transient increases in PO_2 caused by sudden increases in depth. For each dive profile, investigators measured PO_2 continuously and applied Model H95B to the instantaneous PO_2.[30, 31] In 2148 dives to which the model was applied, no diver reported any symptoms. However, the overall predicted incidences of dive-stopping symptoms of CNS oxygen toxicity were 0.52% for the N_2O_2 MK 16 Mod 1 dives, 1.51% for the MK 16 Mod 1 HeO_2 dives, and 8.03% for the CUMA

HeO_2 dives. (These numbers are the totals of the individual values tabulated in references 30 and 31.) The differences, model to experiment, for these dives for development of decompression tables can be ascribed to three factors: time-varying PO_2 profiles, poor predictive power of the models for low incidence of CNS oxygen toxicity, and metabolic rate during decompression lower than that assumed in the model.

PROBABILITIES BASED ON DATA

Definite symptoms of CNS oxygen toxicity occurred in none of 682 dives with constant PO_2 less than or equal to 1.7 atm. Probable events occurred in 19 dives and were cause to abort 6 of them. If the dives with variable PO_2 are included, the numbers become 3796 reported dives with no definite and 25 probable CNS events, including 6 that were dive-stopping.

The best descriptions that we have for mild hyperoxia with no inspired or retained CO_2 are those of Tables 6 and 7. The upper 95% confidence interval when the measured incidence was zero was calculated using the "rule of 3/*n*".[53] The equation setting the binomial probability of *n* misses in *n* trials when the probability of a hit is *p* to the α level of 5%,

$$(1-p)^n = 0.05,$$

becomes

$$n \ln (1-p) = \ln (0.05).$$

For small *p*, $\ln (1-p) = -p$, and thus $p = -\ln(0.05)/n = 2.996/n$, often approximated as

$$p = 3/n.$$

The limits listed here were calculated without the approximations, as

$$p = 1 - e^{(\ln(0.05))/n}.$$

The numbers are very similar to 3/*n*.

If the dives performed to develop and test decompression tables can be assumed to be typical dives for the UBAs, the zero incidence of CNS oxygen toxicity allows calculation of overall confidence intervals for dives of all duration permitted by decompression considerations. Despite the overshoots of PO_2, the probability of CNS oxygen toxicity from diving the MK 16 Mod 1 N_2O_2 tables is less than or equal to 1.5% and from diving the HeO_2 tables is less than or equal to 0.4%. The probability of a CNS event while diving the CUMA with HeO_2 is less than or equal to 0.2%. The differences in the risk estimates arise only because of the different numbers of exposures for which data are available.

CONCLUSIONS

Models designed to predict risk of CNS oxygen toxicity perform poorly, particularly for mild hyperoxia where CNS oxygen toxicity is a rare event. Available data do not permit better model construction. It is possible, for example, that a time-averaged PO_2, not the instantaneous PO_2, is the variable of interest. During model development, variables should at least include metabolic rate and arterial CO_2 partial pressure. Unfortunately, both are either approximately constant or unknown across the available data.

Dive conditions for the available mildly hyperoxic dive data vary across dive series. The most important consideration for risk of toxicity appears to be CO_2 retention, whether from excessive work intensity or from rebreather scrubber failure and CO_2 inhalation. Published training dive information[43,49] implicates CO_2 in the higher incidence of CNS oxygen toxicity episodes in training rather than experimental dives, both from scrubber failure and from excessively strenuous work.

Despite oxygen overshoots during descent, controlled-PO_2 rebreather decompression dives have very low risk when CO_2 is well controlled. This class of dives has a short period with elevated metabolic rate, then a long resting period during decompression. For diving with N_2O_2, probability of any CNS toxic event is less than or equal to 1.5%, and with HeO_2, less than or equal to 0.4% for the MK 16 Mod or 0.2% with the CUMA. Long, shallow oxygen swims also carry low risk of CNS oxygen toxicity if CO_2 is well controlled (Table 6). However, if scrubber endurance is pushed to its limits, if swimmers must work too hard, or if UBAs are hard to breathe, the probability of CNS oxygen toxicity increases considerably (Table 5).

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